carrier comprises heparin or a salt thereof.

104. The method according to claim 76, wherein the osteogenic composition further comprises heparin or a salt thereof.

105. The method according to claim 77, wherein the carrier comprises heparin or a salt thereof.--

REMARKS

Applicants have canceled claims 89 and 92 without prejudice, and added new claims 102-105. As such, claims 69-88, 90, 91, and 93-105 are pending in this application. Of these, claims 69, 74, 76, 77, 86, 87, 90, 91, 93, 95, 97, 98, and 100 have been amended to promote clarity and to further define the scope of the invention.

Amendment 1

Applicants have amended claims 69, 74, 76 and 77 to remove the disclaimers, and to specify instead that the MPSF is "selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone." Support for this amendment appears in claim 87 as originally filed and in the specification, e.g., in Figs. 1-12, and in Examples 3-5 and 7-13 (pp. 71-77 and 85-95).

Accordingly, claim 87 has been amended such that its scope is narrower than the scope of its base claim – claim 77.

Amendment 2

Applicants have further amended claims 69, 74, 76, and 77 to replace the term "capable of stimulating" with "being at a concentration effective to stimulate." Thus, the amended claims require that the MPSF be present in the recited composition at an amount effective to stimulate the tissue inductive activity of the morphogenic protein ("MP").

Support for this amendment is found in the alkaline phosphatase ("AP") assay results shown in Figures 1-10 and discussed at pp. 34-35 and 37 of the specification. The alkaline assay method is described at p. 34, lines 12-18:

> First, a MPSF is identified by picking one or more concentrations of a MPSF and testing them alone or in the presence of a morphogenic protein (**Examples 3 and 4**). Second, the amount of MPSF required to achieve optimal, preferably synergistic, tissue induction in concert with the morphogenic protein is determined by generating a dose response curve (**Example 3**). (boldface original; underscore added)

The results of the AP assays demonstrate that when present at certain concentrations, IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone is capable of stimulating the tissue inductive activity of a morphogenic protein. (see also discussions below).

Amendment 3

Applicants have amended claim 86 to replace the term "dimer" with "dimeric species" and to claim proper dependency from claim 78. Support for this

amendment appears in claim 78 as originally filed and in the specification on p. 12, lines 14-17. This amendment responds to the Examiner's comments in the Office Action on p. 5, lines 4-5.

Amendment 4

Applicants have amended claim 90 to replace "present at a concentration of" with "present in the pharmaceutical composition at a concentration of." This amendment addresses the Examination's comments that it is unclear where the compound is "present." Office Action, p. 5, lines 6-8.

Amendment 5

Applicants have amended claims 91, 93, 95, 97, 98, and 100 to replace "comprises" with "is." The claims are also amended to specify that the recited OP-1 and MPSF concentrations are relative to the pharmaceutical composition in which the OP-1 and MPSF are present.

These amendments respond to the Examiner's comments on claim 91 at p. 5, lines 9-15 of the Office Action, where the Examiner contends that a protein cannot "comprise" a protein and a factor cannot "comprise" a factor, and that it is unclear what the reference for the recited concentrations is.

Amendment 6

Applicants have added claims 102-105 to further define and narrow the scope of their respective base claims -- claims 69, 74, 76, and 77. Support for these claims appears in the specification at p. 49, lines 9-12.

Amendment 7

Applicants have further amended claim 76 to correct an informality: "TGF-b" has been changed to "TGF-β." This amendment responds to the Examiner's comments at p. 2, ¶ 4 of the Office Action.

Amendment 8

Claims 69, 74, and 77 have been further amended to recite the result to be achieved by the process step. This recitation relates back to the claim preamble. This amendment is made in response to the Examiner's § 112, ¶ 2 rejection set forth at p. 5, last ¶.

None of the above amendments introduces new matter. Applicants respectfully request reconsideration of the pending claims in light of the above amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, 1st ¶

I

Claims 69-71, 74-80, 83-87, 90, and 91 stand rejected for alleged lack of enablement. Specifically, the Examiner states that the specification does not reasonably provide enablement for a method of inducing formation, repair or integration of tissues other than bone and that the tissue-inductive functions of various morphogenic proteins are unpredictable. The Examiner cites several references to support the notion of unpredictability, one of which is actually not

prior art.* Office Action, pp. 3-4. Applicants respectfully traverse this rejection.

At the time of applicants' invention, it had been well established in the art that various morphogenic proteins could induce formation of non-bone tissues. For instance, BMP-12 and BMP-13 were known to induce ectopic formation of tendon/ligament-like tissue when implanted in mammals (see the specification at p. 13, lines 11-14). And a method for assaying tendon/ligament-like tissue formation is taught in the specification (Example 12, pp. 93-94). It was also known that BMP-2 and OP-1 induced the differentiation of embryonic mouse cells into astrocyte-like (glial) cells, which are progenitor cells of the nervous system (see the specification at p. 13, lines 20-24). In fact, BMP-2 was shown to stimulate peripheral nerve regeneration. *Id.* A method for assaying nerve regeneration and repair using an *in vivo* rat model is taught in the specification (Example 13, pp. 94-95).

What the prior art did not teach, however, is that an MPSF of the claimed invention, i.e., IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone, can stimulate the ability of these morphogenic proteins in inducing tissue formation and repair. And that is what applicants are claiming.

Thus, based on the prior art, a skilled person in the art would know

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* These references are Kingsley, *Genes & Development* 8:133-146 (1994); Shah et al., *J Cell Sci* 108:985-1002 (1995); Vukicevic et al., *Proc. Natl. Acad. Sci. USA* 93:9021-6 (1996); Nathan et al., *J Cell Biol* 113:981-6 (1991); and Alberts et al. (eds), *Molecular Biology of the Cell*, 3rd Ed. This application claims priority from USSN 08/570,752, filed December 12, 1995. Thus, Vukicevic is not prior art.

what morphogenic protein to use to induce formation of a given tissue type. And based on the guidance provided by applicants' disclosure, he/she would know how to determine an MPSF concentration effective to stimulate the tissue inductive activity of this morphogenic protein.

The Examiner further contends that the specification does not teach how to replace permanent cells such as nerve cells. As pointed out above, the specification does teach how to replace nerve cells in, e.g., Example 13.

Rejection Under 35 U.S.C. § 112, 2nd ¶

Claims 69, 74, 75, 77-80, 83-87, 90, and 91 stand rejected as allegedly indefinite. Office Action, p. 5.

The Examiner contends that several terms in claims 86, 90, and 91 are indefinite. Further, claims 69, 74, 75, 77-80, 83-87, 90, and 91 are allegedly indefinite because they "lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved" (p. 5, lines 16-17). Applicants have amended these claims to obviate the rejections (*supra*).

Rejection Under 35 U.S.C. § 102(b)

Claims 69-71, 77-80, and 83-87 stand rejected as allegedly anticipated by Wang (U.S. Patent 5,166,058). According to the Examiner, Wang teaches that BMP-2 may be used to induce bone formation in conjunction with other BMPs or various growth factors such as EGF, PDGF, TGF-α and -β, and

IGF such as IGF-I. Office Action, pp. 6-9. Applicants respectfully traverse in view of the claim amendments.

Amended claims 69-71, 77-80, and 83-87 specify that the MPSF be selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone, and that the MPSF be present at a concentration effective to stimulate the MP's activity.

Wang does not teach the use of growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone to stimulate BMP-2 activity. In fact, the names of these agents do not even appear in Wang.

Wang does mention IGF-I in col. 7, line 38. The context is: "The addition of other known growth factors, such as IGF-I (insulin like growth factor I), to the final composition, may also effect the dosage [of BMP-2]." However, this in no way amounts to a teaching of the use of IGF-I at a concentration effective to stimulate BMP-2 activity, as required by the amended claims. Wang teaches that IGF-I can be added because it is "beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question" (col. 6, lines 33-36). But Wang does not teach that IGF-I has more than additive effects on the bone-inductive activity of a BMP.*

As demonstrated in Fig. 3 of applicants' disclosure, IGF-I has a stimulatory effect on BMP-7 (OP-1) at a concentration of 10 ng/ml or higher in an

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* Wang does not address the manner in which a growth factor acts.

AP assay. When IGF-1 is used alone at 10, 25, 50, or 100 ng/ml (bottom plot line), the relative AP level, a well established indicator of bone forming activity, does not differ significantly from the background level (100%), where no IGF-I or OP-1 is used. This shows that IGF-I itself does not have a direct effect on the AP level. However, when IGF-I is used in conjunction with OP-1, it significantly increases the AP-inducing activity of OP-1. For instance, when OP-I is used alone at 200 ng/ml, the relative AP level is 450%. When IGF-1 is added at 25 ng/ml, the relative AP level is increased to about 820%. These results demonstrate that while IGF-I itself does not have an effect on the AP level, it can stimulate the AP-inducing activity of a morphogenic protein such as OP-1.

Nowhere in Wang is this taught. Wang at most discloses the use of certain growth factors that are beneficial to bone formation. Wang does not teach that IGF-I can stimulate BMP-2 activity, as required by the amended claims. The Examiner alleges that Wang teaches using IGF-I "in an amount capable of synergistically stimulating the ability of the BMP to induce bone formation because 'it is expected that BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors,' and as evidenced by Baylink (a7) . . . ." (p. 8, line 17 to p. 9, line 1). The Examiner is in error.

Wang is ambiguous as to whether IGF-I synergistically stimulates BMP-2. It says that BMP-2 "**may** act in concert with or **perhaps** synergistically with" other growth factors. This statement is full of uncertainty. It is a mere speculation. It does not teach which growth factor acts merely "in concert" and

which factor acts synergistically with BMP-2. Based on this scant disclosure, a person of ordinary skill in the art would not have known whether IGF-I acts synergistically with BMP-2.

Indeed, while Wang mentions the combined use of TGF-β and IGF with BMP-2 (col. 6, lines 39-40), applicants discovered and disclosed that TGF-β and IGF-II actually **do not** act synergistically with a BMP (*infra*). TGF-β was said to have certain bone growth activity. But applicant showed that TGF-β1 does not stimulate OP-1-induced osteogenic induction. On the contrary, it inhibits OP-1's activity. See, e.g., Fig. 12 and p. 7, lines 24-32. Further, applicant demonstrates that unlike IGF-I, IGF-II cannot stimulate OP-1-induced osteogenic induction. See, e.g., Fig. 11 and p. 7, lines 16-23.

In short, Wang provides no teaching on the ability of IGF-I to stimulate an MP's activity.

As to Baylink (U.S. Patent 5,691,305), it describes the use of FGF, TGF-β, IGF-II and PDGF. It does not even mention IGF-I, much less the use of IGF-I to stimulate an MP. (see also discussions below on Baylink)

Thus, Wang does not anticipate the claimed invention. And Baylink does not change this fact.

Rejection Under 35 U.S.C. § 102(e)

Claims 77 and 85 stand rejected as allegedly anticipated by Kuberasampath (U.S. Patent 5,674,844). According to the Examiner,

Kuberasampath teaches inhibiting bone loss and stimulating bone growth by using morphogens in conjunction with other "cofactors" known to have a beneficial effect on bone remodeling, including IGF-I. The Examiner also contends that the reference teaches using IGF-I "in an amount capable of synergistically stimulating the ability of the OP-1 to induce bone formation as evidenced by" Wang and Baylink. Office Action, pp. 9-11.

Applicants traverse this rejection. Amended claims 77 and 85 require that the MPSF be present at a concentration effective to stimulate the tissue inductive activity of an MP. As discussed above, "stimulate" means that the MPSF would need to have a synergistic effect, i.e., more than the addition of the effects of the MPSF and the MP. Kuberasampath does not teach that.

Kuberasampath is completely silent with respect to the feature that IGF-I (and other MPSFs of the invention, i.e., growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone) can have synergistic effects on a morphogenic protein when present at a certain concentration. The "cofactors", as disclosed by Kuberasampath, are those which are known to have a beneficial effect on bone remodeling, but the term "beneficial" is ambiguous and not clearly defined.

The Examiner alleges that Kuberasampath teaches the use of IGF-I in an amount that synergistically stimulates OP-1 activity, citing Wang and Baylink in support. This is wrong. As discussed above, neither reference teaches the use of synergistic amounts of IGF-I or other MPSFs of the claimed invention.

The Examiner also cites Figure 4 of Kuberasampath for support. However, this figure has nothing to do with MPSF. This figure compares the AP-stimulating activity of OP-1 and TGF-β. Based on the results shown in this figure, the reference concludes that OP-1 alone can stimulate the production of AP in osteoblasts (col. 24, lines 28-34). This figure does not teach mixing OP-1 and TGF-β. At any rate, TGF-β is not an MPSF claimed in the present invention.

In sum, Kuberasampath fails to anticipate claim 77 or 85.

Rejections Under 35 U.S.C. § 103(a)

I

Claims 74 and 75 stand rejected as allegedly obvious over Wang in view of Kuberasampath (U.S. Patent 4,968,590). The claims are directed to a method of accelerating allograft repair and incorporation in a mammal using a matrix-comprising device comprising an MP and an MPSF, where the matrix may comprise allogenic bone. The Examiner alleges that it would have been obvious to a person skilled in the art at the time of applicants' invention to arrive at the claimed invention by using a composition containing a therapeutically effective amount of BMP-2, IGF-I and a matrix, as taught by Wang, and using allogenic bone as matrix as taught by Kuberasampath.

As discussed above, Wang does not teach or suggest the use of the claimed MPSF at a concentration effective to stimulate a morphogenic protein to induce tissue formation. Kuberasampath, cited by the Examiner for teaching bone

matrix, does not remedy this deficiency. Indeed, the Examiner acknowledges that Kuberasampath is silent with respect to the use of BMP-2 and IGF-I to induce bone formation. Thus, a combination of Wang and Kuberasampath fails to render obvious the claimed methods in which the claimed MPSF must be present at a concentration effective to stimulate the tissue inductive activity of an MP.

II

Claim 76 stands rejected as allegedly obvious over Rueger (U.S. Patent 5,344,654) in view of Wang. Office Action, pp. 14-18. Applicants respectfully traverse this rejection.

Claim 76 is directed to a method of promoting *in vivo* integration into a target tissue of an implantable prosthetic device. The device comprises an MP and an MPSF that is present at a concentration effective to stimulate the tissue inductive activity of the MP.

As discussed above, Wang does not teach the use of a composition containing an MP and an MPSF that is at a concentration effective to stimulate the activity of the MP. Rueger, which is cited for teaching prosthetic devices coated with substantially pure osteogenic protein, does not remedy this deficiency. Thus, the Examiner has not established a *prima facie* case of obviousness regarding claim 76.

III

Claims 77, 90 and 91 stand rejected as allegedly obvious over Kuberasampath (U.S. Patent 5,674,844) as applied to claim 77 above and further in

view of Hock (Hock et al., *Endocrinology* 122:254-60 (1988)) and further in view of Baylink or Wang.

According to the Examiner, Kuberasampath discloses the administration of morphogens, such as OP-1, together with other "cofactors" known to have a beneficial effect on bone remodeling, including IGF-I. Office Action, p. 19, lines 5-9. In the Examiner's view, Hock teaches that IGF-I increases the bone matrix apposition rate at 75 ng/ml. On this basis, the Examiner concludes

> Although Kuberasampath (e7) in view of Hock are silent with respect to the synergistic action of OP-1 and IGF-I, no difference is seen between a synergistic combination of the two, the concentrations recited in the instant claims, and the concentration taught by the prior art. Burden is shifted to Applicants to distinguish between the two. (p. 21, lines 12-15; emphasis added)

But as amended, claims 77, 90, and 91 require that the MPSF such as IGF-I exist in the pharmaceutical composition at a concentration effective to stimulate the tissue inductive activity of an MP. The ability of the claimed MPSF to stimulate that activity is unexpected. It is not taught by the two references, as admitted by the Examiner (see underscored portion of the above quote).

As to Baylink, the Examiner alleges that it teaches promoting bone growth and healing of osseous defects with a composition containing at least two of BMP, FGF, TGF-β, IGF-II and PDGF. The Examiner states that this composition "not only has an additive effect on the proliferation and differentiation of bone cells, but creates a surprisingly marked synergism as well" (Office Action, p. 22, lines 4-7).

But Baylink does not even mention IGF-I, or any of the remaining MPSFs specified in claims 77, 90 and 91. The alleged teaching that two or more* of BMP, FGF, TGF-β, IGF-II and PDGF may create synergism does not foreshadow that IGF-I has synergism with an MP. Baylink provides no more than a motivation to try other growth factor combinations (if it does at all), but it provides no reasonable expectation of success. In fact, it is not known from Baylink whether all 25 random combinations of two or more of BMP, FGF, TGF-β, IGF-II and PDGF create synergism. Its limited working examples (cols. 3 and 4) provide no answer.

Indeed, not every growth factor acts synergistically with an MP. Applicants discovered that TGF-β and IGF-II in fact do not act synergistically with MPs. TGF-β even inhibits BMP activity (*supra*). Thus, by generally describing the use of TGF-β and IGF-II with a BMP, Baylink does not teach that IGF-I or any other MPSFs specified in the rejected claims can be used synergistically with an MP.

The Examiner also cites Wang in support of his *prima facie* case of obviousness. Applicants have set forth above that this reference does not teach synergism, which is now a claim element.

Information Disclosure Statement

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* Baylink actually prefers a combination of four factors. Col. 2, line 37.

The Examiner states that the IDS filed April 7, 1999 fails to comply with the provisions of 37 C.F.R. §§ 1.97 and 1.98 and MPEP § 609 and that copies of the cited documents in the IDS were not present in parent application USSN 09/027,873.

Accordingly, applicants submit the enclosed new IDS, Form PTO-1449, and copies of the documents listed thereon.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance to the pending claims.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 on July 16, 2001

Claire V. Driscoll

Signature of Person Signing

Appendix of Amended Claims

69. (Twice Amended) A method for inducing local tissue formation from a progenitor cell in a mammal comprising the step of implanting in the mammal a morphogenic device at a locus accessible to at least one progenitor cell of the mammal, whereby the morphogenic device induces local tissue formation from the progenitor cell in the mammal, [wherein] the morphogenic device [comprises] comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of hormones, cytokines, peptides and growth factors disposed in the carrier, the stimulatory factor [capable of stimulating] being at a concentration effective to stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell,

[with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin;

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D;

when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone.]

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone.

74. (Twice Amended) A method of accelerating allograft repair and incorporation in a mammal, comprising the step of implanting at a locus in need of replacement bone a matrix-comprising device, whereby the device accelerates allograft repair and incorporation in the mammal, the device comprising:

a) an implantable biocompatible carrier,

b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and

c) a morphogenic protein stimulatory factor (MPSF) selected from the group consisting of hormones, cytokines, peptides and growth factors disposed

in the carrier, the stimulatory factor [capable of stimulating] being at a concentration effective to stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell,

[with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin;

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D;

when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone.]

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone.

76. (Twice Amended) A method of promoting in vivo integration into a target tissue of a mammal an implantable prosthetic device, the method comprising the steps of:

a) providing on a surface of the prosthetic device an osteogenic composition, and

b) implanting the device in a mammal at a locus where the target tissue and the surface of the prosthetic device are maintained at least partially in contact for a time sufficient to permit enhanced tissue growth between the target tissue and the device,

wherein the osteogenic composition comprises (1) an morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and (2) a morphogenic protein stimulatory factor (MPSF) [capable of stimulating] at a concentration effective to stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell, said morphogenic protein and MPSF disposed on the surface region in an amount sufficient to promote from a progenitor cell enhanced tissue growth between the target tissue and the device;

[with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin;

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-b, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D;

when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-b; and

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone.]

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone.

77. (Twice Amended) A method of treating a tissue degenerative condition in a mammal comprising the step of administering a pharmaceutical composition to the mammal, whereby the composition treats the tissue degenerative condition in the mammal, the composition comprising:

a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor selected from the group consisting of hormones, cytokines, peptides and growth factors, said factor [capable of stimulating] being at a concentration effective to stimulate the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier;

[with the proviso that when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is activin, the MPSF may not be estrogen or calcitonin;

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a BMP homodimer or TGF-β, the MPSF may not be FGF, IGF-II, PDGF, estrogen, calcitonin or vitamin D;

when the progenitor cell is an osteoblast stimulated to form bone or cartilage and the morphogenic protein is a BMP homodimer, the MPSF may not be TGF-β; and

when the progenitor cell is an osteoblast stimulated to form bone and the morphogenic protein is a homodimer of BMP-2 or BMP-3, the MPSF may not be parathyroid hormone.]

wherein the MPSF is selected from the group consisting of IGF-I, growth hormone, hydrocortisone, insulin, parathyroid hormone and progesterone.

86. (Amended) The method according to claim [79] 78, wherein the [dimer] dimeric species is a homo- or [a heterodimer] hetero-dimer comprising at least one BMP-2 or OP-1 (BMP-7) subunit.

87. (Amended) The method according to claim 77, wherein the morphogenic protein stimulatory factor [comprises at least one compound selected from the group consisting of: insulin-like growth factor I (IGF-I), estradiol, fibroblast growth factor (FGF), growth hormone (GH), growth and differentiation factor (GDF), hydrocortisone (HC), insulin, progesterone, parathyroid hormone (PTH), vitamin D, retinoic acid and IL-6] is IGF-I.

Delete claim 89 without prejudice.

90. (Amended) The method according to claim 77, wherein the morphogenic protein is present in the pharmaceutical composition at a concentration of at least about 1 ng/ml, and the morphogenic protein stimulatory factor is present in the pharmaceutical composition at a concentration of at least about 0.01 ng/ml.

91. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is IGF-I and is present in the pharmaceutical composition at a concentration of from about 0.1 ng/ml to about 50 ng/ml.

Delete claim 92 without prejudice.

93. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is a growth hormone and is

present in the pharmaceutical composition at a concentration of from about 5 ng/ml to about 1000 ng/ml.

95. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is hydrocortisone and is present in the pharmaceutical composition at a concentration of from about 0.05 nM to about 5.0 nM.

97. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is insulin and is present in the pharmaceutical composition at a concentration of from about 0.01 nM to about 1000 nM.

98. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is parathyroid hormone and is

present in the pharmaceutical composition at a concentration of from about 10 nM to about 1000 nM.

100. (Amended) The method according to claim 77, wherein the morphogenic protein [comprises] is OP-1 and is present in the pharmaceutical composition at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor [comprises] is progesterone and is present in the pharmaceutical composition at a concentration of from about 0.05 nM to about 1000 nM.

Please add new claims 102-105.

--102. The method according to claim 69, wherein the carrier comprises heparin or a salt thereof.

103. The method according to claim 74, wherein the carrier comprises heparin or a salt thereof.

104. The method according to claim 76, wherein the osteogenic composition further comprises heparin or a salt thereof.

105. The method according to claim 77, wherein the carrier comprises heparin or a salt thereof.--